09/753278

PCT KR00 01171

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day month year) 27 June 2001 (27.06.01)	
International application No. PCT/KR00/01171	**Applicant's or agent's file reference** #137
International filing date (day month year) 18 October 2000 (18.10.00)	**Priority date** (day month year) 18 October 1999 (18.10.99)
Applicant PARK, Jai, Wook et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 May 2001 (02.05.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

KR0001171

COPY FOR IB

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference #137	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT IPEA 416)
International application No. **PCT/KR00/01171**	International filing date *(day month year)* 18 OCTOBER 2000 (18.10.2000)	Priority date *(day month year)* 18 OCTOBER 1999 (18.10.1999)

International Patent Classification (IPC) or national classification and IPC

IPC7 C07C 67/00, C12P 7/00

Applicant

Samsung Fine Chemicals Co., Ltd. et al

1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2 This REPORT consists of a total of 3 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and or drawings which have been amended and are the basis for this report and or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3 This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
02 MAY 2001 (02.05.2001)	25 JANUARY 2002 (25.01.2002)

Name and mailing address of the IPEA/KR	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 920 Dunsan-dong, Seo-gu, Daejeon Metropolitan City 302-701, Republic of Korea	KANG, Jeon Kwan
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-5553

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT KR00 01171

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[ ] the description:
pages _____ . as originally filed
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

[ ] the claims:
pages _____ . as originally filed
pages _____ . as amended (together with any statment) under Article 19
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

[ ] the drawings:
pages _____ . as originally filed
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

[ ] the sequence listing part of the description:
pages _____ . as originally filed
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language English which is

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[X] the language of publication of the international application(under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and or 55.3).

3. With regard to any **nucleotide** and or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained inthe international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international applicationas as filed has been furinshed.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages _____

[ ] the claims Nos. _____

[ ] the drawings, sheet _____

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box(Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT KR00 01171

V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Statement

Novelty (N)	Claims	1-9	YES
	Claims		NO
Inventive step (IS)	Claims	1-9	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims		NO

2 Citations and explanations (Rule 70.7)

The invention defined by the claims is a process for preparing a chiral ester(100) by mixing and reacting the following materials:

1.a ketone(4)
2.a ruthenium complex(1,2,3)to reduce said ketone(4) to a racemic alcohol and to activate racemization of said racemic alcohol
3. a lipase to acylate one enantiomer selectively from said racemic alcohol
4.a hydride donor group to supply hydride group to said ruthenium complex(1,2,3)
5.an acyl donor group to supply acyl group to said lipase

No individual citation or obvious combination of citations discloses this process for preparing a chiral ester(100).

The closest art is EP-A2-375417. Although this is directed to a process for preparing a chiral ester, the method employed is different to the present invention.

Therefore the subject matter of claims 1-9 meets the requirements of Article 33(2)-(4).

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PCT REQUEST

#137

Original for SUBMISSION - printed on 18.10.2000 03:53:21 PM

0 0-1	**For receiving Office use only** International Application No	PCT/KR 00/01171
0-2	International Filing Date	18 October 2000 (18.10.00)
0-3	Name of receiving Office and "PCT International Application"	Korean Industrial Property Office PCT International Application
0-4 0-4-1	**Form - PCT/RO/101 PCT Request** Prepared using	PCT-EASY Version 2.91 (updated 06.12.1999)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Korean Industrial Property Office (RO/KR)
0-7	**Applicant's or agent's file reference**	#137
I	**Title of invention**	METHOD FOR PREPARING CHIRAL ESTER
II II-1 II-2 II-4 II-5 II-6 II-7 II-8 II-9	**Applicant** This person is Applicant for Name Address State of nationality State of residence Telephone No Facsimile No	applicant only all designated States except US Samsung Fine Chemicals Co., Ltd. 190, Yeocheon-dong Nam-ku 680-090 Ulsan Republic of Korea KR KR 82-2-772-1742 82-2-772-1749
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	**Applicant and/or inventor** This person is Applicant for Name Address State of nationality State of residence	applicant only all designated States except US Pohang University of Science and Technology San 31, Hyoja-dong Nam-ku, Pohang-si 790-784 Kyongsangbuk-do Republic of Korea KR KR

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III-2	**Applicant and/or inventor**	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	PARK, Jai Wook
III-2-5	Address	6-501, Professor Apt., 756 Jigok-dong, Nam-ku, Pohang-si 790-390 Kyongsangbuk-do Republic of Korea
III-2-6	State of nationality	KR
III-2-7	State of residence	KR
III-3	**Applicant and/or inventor**	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	KIM, Man-Joo
III-3-5	Address	6-1405, Professor Apt., 756 Jigok-dong, Nam-ku, Pohang-si 790-390 Kyongsangbuk-do Republic of Korea
III-3-6	State of nationality	KR
III-3-7	State of residence	KR
III-4	**Applicant and/or inventor**	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	KOH, Jeong Hwan
III-4-5	Address	12-213,Pohang University of Science and Technology Dormitory, 756 Jigok-dong, Nam-ku, Pohang-si 790-390 Kyongsangbuk-do Republic of Korea
III-4-6	State of nationality	KR
III-4-7	State of residence	KR
III-5	**Applicant and/or inventor**	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	JUNG, Hyun Min
III-5-5	Address	3-403, Graduate Apt., 756 Jigok-dong, Nam-ku, Pohang-si 790-390 Kyongsangbuk-do Republic of Korea
III-5-6	State of nationality	KR
III-5-7	State of residence	KR

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IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby has been appointed to act on behalf of the applicant(s) before the competent International Authorities as	agent
IV-1-1	Name (LAST, First)	HUH, Sang Hoon
IV-1-2	Address	13th Fl. Hyecheon Bldg, 831, Yeoksam-dong Kangnam-ku 135-792 Seoul Republic of Korea
IV-1-3	Telephone No	82-2-553-1331
IV-1-4	Facsimile No	82-2-557-1290
IV-1-5	e-mail	hallalaw@kornet.net
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

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V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit		
V-6	**Exclusion(s) from precautionary designations**	NONE	
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	18 October 1999 (18.10.1999)	
VI-1-2	Number	1999-45041	
VI-1-3	Country	KR	
VII-1	**International Searching Authority Chosen**	Korean Industrial Property Office (KIPO) (ISA/KR)	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	5	-
VIII-2	Description	13	-
VIII-3	Claims	6	-
VIII-4	Abstract	1	#137.txt
VIII-5	Drawings	0	-
VIII-7	TOTAL	25	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-12	Priority document(s)	Item(s) VI-1	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**		
VIII-19	**Language of filing of the international application**	Korean	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name (LAST, First)	HUH, Sang Hoon	

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10-1	**Date of actual receipt of the purported international application**	18 October 2000 (18.10.00)
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	

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Original (for **SUBMISSION**) - printed on 18.10.2000 03:53:21 PM

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/KR
10-6	Transmittal of search copy delayed until search fee is paid	

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11-1	Date of receipt of the record copy by the International Bureau	14 NOV 2000	(14.11.00)

키랄 에스테르의 제조방법

(Method for preparing chiral ester)

【발명이 속하는 기술분야 및 그 분야의 종래기술】

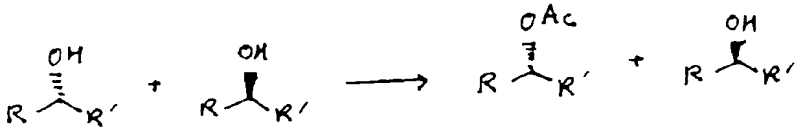
본 발명은 키랄 에스테르의 제조방법에 관한 것으로서, 보다 상세하게는 효소와 금속 촉매를 이용하여 케톤으로부터 키랄 에스테르를 제조하는 방법에 관한 것이다.

광학순도 특성이 우수한 화합물을 입체 선택적으로 합성하는 기술은 유기합성에서 가장 중요한 분야중의 하나로서, 특히 금속 촉매 반응과 효소 촉매를 이용한 비대칭 합성에 대한 연구가 활발하게 이루어지고 있다.

오늘날, 효소 촉매를 이용하여 라세믹 기질을 속도론적 광학 분할하는 방법은 유기 합성에서 기본적으로 많이 이용되고 있다. 특히, 리파아제-촉매하에서의 에스테르의 가수분해 및 알콜의 아실화 반응에 관한 다양하고 효율적인 방법들이 많이 알려진 상태이다.

속도론적 광학 분할 반응은, 일반적으로 라세믹 혼합물의 두 개의 에난쇼머(enantiomer)가 상이한 속도로 생성물로 변화되는 반응으로 정의된다. 따라서, 이러한 광학 분할 방법에서는 하기 반응식 1에서와 같이 라세믹 혼합물의 에난쇼머중의 하나가 선택적으로 생성물로 변화되고 나머지 에난쇼머는 잔류하게 된다.

【반응식 1】



한편, 케톤으로부터 키랄 에스테르를 얻는 방법으로는, 케톤을 엔올 에스테르(enol ester)로 변화시킨 다음, 이를 비대칭 수소화반응을 통하여 환원하는 방법, 케톤을 비대칭 수소화 반응 등을 거쳐 환원하여

적당 안정으로 변화한 따름, 에스테르화하는 방법이 있다. 그러나 상기 종래의 방법들은 모두 적어도 2 이상의 반응 단계를 거쳐야 제품으로부터 얻을 에스테르를 얻을 수 있으므로 그 제조과정이 상당히 복잡한 점이다.

【발명이 이루고자 하는 기술적 과제】

본 발명이 이루고자 하는 기술적 과제는 상기 문제점을 해결하여 제조공정이 단순화되면서도 완화조건 및 합성수율이 우수한 카복시에스테르를 제조할 수 있는 방법을 제공하는 것이다.

【발명의 구성】

상기 기술적 과제를 이루기 위하여 본 발명에서는, 제공과,

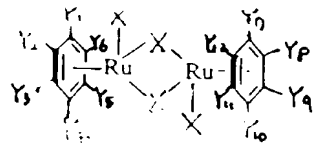
상기 제품을 디세틸 알콜과 환원시키는 반응과 상기 디세틸 알콜의 디세틸화 반응을 순차적키는 단속화물, 상기로는 루테늄을 촉매, 더욱 바람직하기로는 화학식 1 내지 3의 루테늄 촉매를 사용과,

상기 디세틸 알콜의 하나의 에틸소비를 선택적으로 아실화시키는 디아세틸화,

상기 루테늄 촉매에 하이드라이드를 공급하는 하이드라이드 모니와,

상기 디아세틸에 아실기를 공급하는 아실 모니를 존재 및 반응시키는 것을 특징으로 하는 카복시에스테르의 제조방법을 제공한다.

[화학식 1]

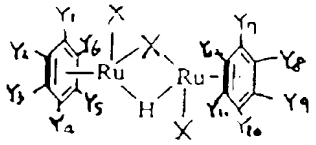


상기식중, Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}는 서로에 관계없이 탄화수소를 나타내거나, 수소 또는 탄소수 1 내지 5의 알킬기를

나타내고

X는 Br, Cl 또는 I이고,

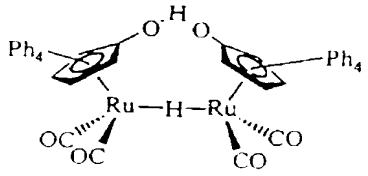
[화학식 2]



상기 식중, Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}는 서로에 관계없이 독립적으로 수소 또는 탄소수 1 내지 5의 알킬기를 나타내고

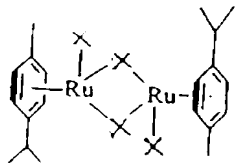
X는 Br, Cl 또는 I이다.

[화학식 3]

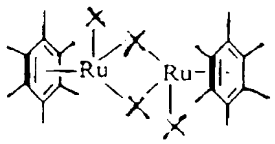


상기 루테늄 착물을 하기 화학식 5-10으로 표시되는 화합물 중에서 선택되는 것이 보다 바람직하다. 특히 하기 화학식 5-10에서, X는 Cl, Br 또는 I이며, Cl인 것이 가장 바람직하다.

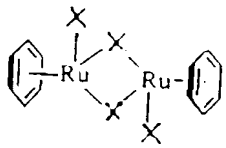
【화학식 5】



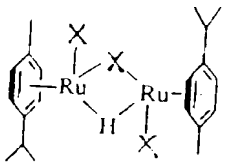
【화학식 6】



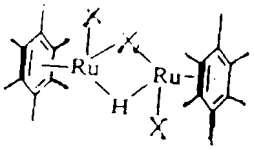
【화학식 7】



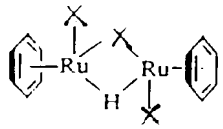
【화학식 8】



【화학식 9】



【화학식 10】



본 발명의 1단계 반응은 용매에 화학식 1의 케톤으로부터 화학식 100의 키랄 에스테르를 제조하는 방법을 설명하면 다음과 같다.

먼저, 화학식 1 내지 3의 루테늄 착물, 디아세틸, 하이드라이드 보다, 아실기 보다 및 케톤을 용매에 용해한 다음, 여기에 적절한 용매와 염기를 투입하여 이를 반응시킨다(반응식 2). 이 때 반응조건은 사용하는 루테늄 착물의 구조에 따라 달라진다. 즉, 화학식 5의 루테늄 착물(X=Cl)을 사용하는 경우에는 반응 온도는 10 내지 50℃이고, 화학식 6의 루테늄 착물(X=Cl)을 사용하는 경우에는 반응 온도는 10 내지 50℃이고, 화학식 8의 루테늄 착물을 사용하는 경우에는 반응 온도는 70

내지 100℃이다. 또한 화학식 2의 화합물을 상업적으로 수득하기 어려울 경우, 상기 범위 내의 조건하에서 화학식 2의 화합물을 수득하기 위한 반응을 선행하는 것이 바람직하다. 화학식 2의 화합물을 함유하는 시료를 사용할 때 얻어지는 광학 선택도 값이 중요하다. 또한 상기 화합물 함량의 완만한 제품을 기준으로 하여 0.1 배지 고정한 것이 바람직하다. 만약 화합물 함량이 고정량 범위보다 많은 경우에는 재결정에 의해 정제하고 0.1중량% 미만인 경우에는 반응이 느려지므로 바람직하지 못하다.

【반응식 2】

(화학식 4) (화학식 100)

상기식중, R_1, R_2 및 R_3는 서로 독립적으로 비치환된 또는 치환된 알킬기, 비치환된 또는 치환된 아릴기, 비치환된 또는 치환된 사이클로알킬기 이루어진 군으로부터 선택되고, 경우에 따라서 R_1과 R_2, R_2과 R_3, R_1과 R_3는 서로 연결된 형태일 수 있다. 여기에서 알킬기, 아릴기 및 사이클로알킬기에 치환가능한 작용기로는 알콕시 원소와 같은 헤테로 원자, 시안(CN)기 등이 가능하다.

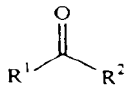
상기 반응에서 화학식 2의 화합물을 유효 전달 반응의 촉매로 작용하여 광학적인 제품을 더해서 얻어지는 반응을 촉진시킨다. 여와 아울러 얻어진 더해된 알코올과 더해여와 반응을 촉진시킨다.

상기 리파아제는 에스테르의 가수분해 효소로서, 더해된 알콜의 하나의 에난티오머를 선택적으로 아실화시켜 광학적으로 순수한 저급 에스테르를 생성시키는 작용을 한다. 이러한 리파아제의 구체적인 예로는 캔디다 안타르티카 리파아제(*candida antarctica* lipase), 슈도모나스 세파시아스 리파아제(*Pseudomonas cepacias* lipase)등에서

실시하여, 바람직하게는 캔디다 안타르티카 유래 B 리파아제 및 슈도모나스 세파시아스 리파아제 중 아크릴 레진(*candida antarctica* component B lipase supported on acrylic resin)(상품명: Novozym 435(Novo사), 슈도모나스 세파시아스 리파아제 시료(*Pseudomonas cepacias* lipase supported on ceramic particle)(상품명: Lipase PS-C)(Amano사)이며, 보다 바람직하게는 캔디다 안타르티카 유래 B 리파아제 시료(상품명: Novozym 435(Novo사))를 사용하는 것이, 안전성, 반응성, 화학수율 등의 측면에서 더욱 바람직하다. 또한 리파아제의 함량은 노르보르넨의 경우에는 예를 들면 1mmol당 10 내지 60mg, 바람직하게는 30mg을 사용하며, 리파아제 PS-C의 경우는 예를 들면 1mmol당 10 내지 200mg, 바람직하게는 50mg을 사용한다.

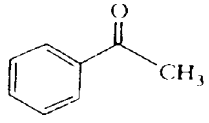
상기 제품을 일반적으로는 화학식 1로 표시되는 것으로서 그 구조가 특별히 제한되지는 않으나, 본 발명에서는 하기 화학식 1a-g의 화합물을 사용한다.

【화학식 1】

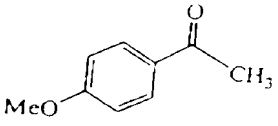


여기서 R_1, R_2, R'는 상기 반응식 2에 정의한 바와 같다.

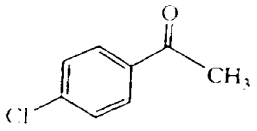
【화학식 1a】



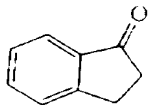
【화학식 1b】



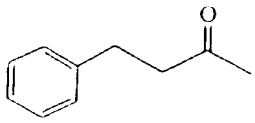
【화학식 1c】



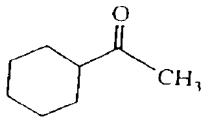
【화학식 1d】



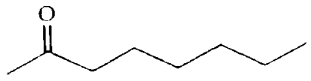
【화학식 1e】



【화학식 1f】



【화학식 1g】



상기 아실 모니모는 티오아세에 아실기를 공급하여 티오아세 중에하의 아실 전이 반응에서의 입력을 아실화된 생성물쪽으로 이동시키는 역할을 한다. 이러한 아실 모니모는 아릴 에스테르 또는 알케닐 아세테이트가 바람직하며, 특히 전자흡용성기(electron withdrawing group)를 갖고 있는 아릴 에스테르 예를 들어, p-클로로페닐 아세테이트가 가장 바람직하다. 그리고 알케닐 아세테이트의 예로는 이소프로페닐 아세테이트가 있다. 이러한 화합물이 아실 모니모로서 바람직한 이유는 작절한 반응성을 가지면서 아세테화 반응을 방해하지

[illegible] 제공한다. [illegible] 상기 [illegible] 화합물 제품 1단위는 [illegible] 화합물 1개의 단위인 것이 바람직하다. 여기에서 아실 [illegible]의 [illegible] 1단위는 [illegible] 상기 [illegible] 분자에 공제적 결합, 2단위 이상인 경우 제품 아실의 반응속도가 감소하여 바람직하지 못하다.

본 발명의 하이드라이드 [illegible]는 촉매를 활용에 하이드라이드를 [illegible] 역할을 한다. 하이드라이드 [illegible]의 공제적인 예에는 [illegible]-디메틸셀렌-1-옥, 산소, 메타신 등이 있다. 이 하이드라이드 [illegible]의 화합물 제품은 기준으로 하여 1 내지 2단량인 것이 바람직하다. 여기에서 하이드라이드 [illegible]의 화합이 상기 범위를 벗어나는 경우에는 [illegible] 반응을 방해하여 바람직하지 못하다.

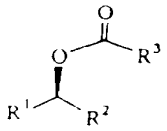
상기 지방 에스테르 제조방법에서 얻어지는 반응혼합 생성된 산화 [illegible], 아연 성분 제거하는 방법은 하여, 공제적인 예로서 아실 [illegible] 디메틸아민, 디메틸포름아미드 등을 사용한다. 이 때 얻기의 화합물 제품은 기준으로 하여 1 내지 2단량인 것이 바람직하다.

본 발명의 용매는 [illegible]되지는 않는다. 다만, 디옥사세와 같은 [illegible] 촉매 반응을 생성물의 유성유를 및 임제 전달성분에서 용매의 일정을 벗는 것이 [illegible]이므로 메틸렌클로라이드, 벤젠, 톨루엔, 에틴 등을 사용하는 것이 바람직하다. 그리고 용매의 화합물 [illegible]해서 기준으로 하여 [illegible] 화합물 0.2-0.3배의 용매 범위내에 [illegible]한다.

상술한 화학식 1 내지 3의 [illegible]를 촉매, 디옥사세, 하이드라이드 [illegible], 아실기 [illegible] 및 제품의 반응이 완성되면, 워크-업(work-up) 과정을 거쳐 지방 에스테르를 얻을 수 있게 된다.

이상과 같이 본 발명에 따라 제조된 지방 에스테르 화합물을 [illegible] 화학식 1aa 내지 [illegible] 구조로 제조되는 것이다.

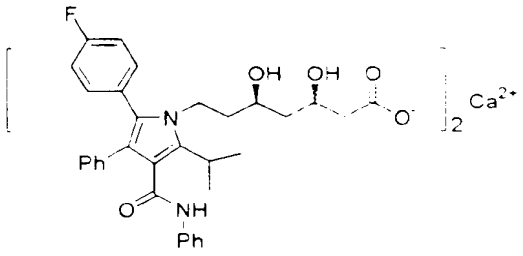
【화학식 100】



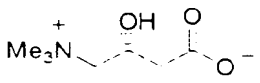
상기 화학식 100에서 R¹, R², 및 R³는 서로 독립적으로 치환된 또는 치환되지 않은 알킬기, 치환된 또는 치환되지 않은 아릴기, 치환된 또는 치환되지 않은 헤테로알킬기 또는 헤테로아릴기로 선택되고, 선택에 따라서 R¹과 R², R²과 R³, 또는 R¹과 R³는 서로 연결된 형태일 수 있다.

바람직한 본 발명에 따른 화학식 100의 지방 에스테라아제 활성 억제제는 지방 합성, 지방 축적, 기타 지방 질환증의 감염에 유효하게 이용될 수 있으며, 구체적으로는 예를 들어 고지혈증 치료제로서 사용되는 화학식 101의 아토르바스타틴(Atorvastatin), 식욕 부진, 허약증의 치료제로 사용되는 화학식 102의 L-카르니틴(L-Carnitine), 에이즈(AIDS) 치료용 약제로 사용되는 화학식 103의 아게네라제(Agonerase) 등의 제조에 원료로 유용하게 사용될 수 있다.

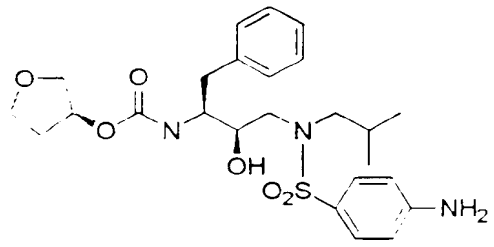
【화학식 101】



【화학식 102】

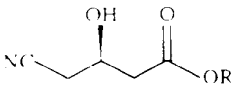


【화학식 101】



상기한 원료의 화합물 중에서 예컨대, 피ravastatin의 원료로서 고부가가치 제조되고 있는 화학식 101의 화합물의 경우는 본 발명에 따른 지방에스테르의 중에서 다음 화학식 100a로 표시되는 지방 화합물을 원료로 하여 예컨대 대한민국 제5,905,953호에 공지된 방법에 의해 제조할 수 있다.

【화학식 100a】



상기 식에서 R은 지방알킬기를 의미한다.

특히, 본 발명에 따라 제조되는 상기 화학식 100의 지방에스테르는 종래의 제법에 비해 미반응 알코올 잔존량이 현저히 감소된 것을 특징으로 하며, 통상적으로 상기 생성되어 있는 최대한 억제하고자 지방에스테르의 함량을 100%에 가깝게 극대화시키려면 미반응 알코올이 5% 정도까지 유지하게 제조되는 것이었다. 따라서 미반응 알코올을 최소화하여 제조 수율이 극대화 되는 효과가 있으며, 위와 같은 고부가가치를 나타내는 화학품 등의 제조원료로 사용하는 경우 미반응 알코올의 존재로 인해 환원시킬 수 있기 때문에 알코올이 매우 중시되는 지방화학 분야, 특히 식품, 화장품 제조분야에서 지방 유도체를 제조하는 광범위한 화학품의 제조 원료로 바람직하게 사용될 수 있는 것이다.

이하, 본 발명을 하기 실시예를 들어 설명하기로 하되, 본 발명이

화학식 1a의 화합물 0.25mmol, 2-브로모에틸아민 0.25mmol, 화학식 3의 화합물 (X=Cl) 0.0130 mmol, 2,6-디메틸벤젠-1-술폰 0.25mmol 및 테트라부틸 암모늄 HSO4 2mg을 물 2.5ml에 용해한 용액에 1.2ml에 용해하여 상온 하에서 3분간 교반하였다. 이어서, 반응 용액에 p-톨루엔술폰산 아세테이트 0.75mmol을 첨가하여 실시예 1과 동일한 방법에 따라 실시하였다.

실온 조건하에서 상기 반응액으로부터 산소를 제거한 다음, 반응 용기를 밀폐하였다. 이후, 반응 용액을 55℃에서 7시간동안 교반하였다.

실시예 2-5

화학식 1a의 화합물 대신 화학식 1b~1e의 화합물을 사용한 것을 제외하고는, 실시예 1과 동일한 방법에 따라 실시하였다.

실시예 6

화학식 1의 R내지 화합물 (X=Cl) 대신 화학식 3의 R내지 화합물 (X=Cl)을 사용한 것을 제외하고는, 실시예 1과 동일한 방법에 따라 실시하였다.

실시예 7-10

화학식 1a의 화합물 대신 화학식 1b-1e의 화합물을 사용한 것을 제외하고는, 실시예 6과 동일한 방법에 따라 실시하였다.

실시예 11

화학식 1a의 화합물 0.25mmol, 화학식 3의 R내지 화합물 (X=Cl) 0.050mmol,

[illegible]-아세톤(셀룰로스-1-용매)(0.5mm) [illegible] 유량 속도 1.5 ml/분, 파장 254nm, 주입 부피 0.75ml의 조건에서 분리하였다. 분리된 0.5ml와 동일하게 [illegible] 하여 [illegible] 하였다.

상온 조건하에서 상기 화합물을 제거한 다음, 반응 [illegible] 하였다. 이어서, 상기 반응 [illegible] 제거하여 표제 화합물을 얻었다.

실시예 12-17

화학식 1a의 제조 대신 화학식 1b~1g의 제조를 사용한 것을 제외하고는, 실시예 11과 동일한 방법에 따라 실시하였다.

상기 실시예 1-5 및 실시예 11-17에 따라 키랄 에스테르를 제조하는 경우, 광학순도 양호의 삼성수율, 키랄 아세테이트의 삼성수율 및 광학순도를 측정하여 하기 표 1에 나타내었다. 이때에서 양호 및 키랄 아세테이트의 삼성수율을 가스 크로마토그래피를 이용하여 분석하였으며, 광학순도는 키랄 고속액체크로마토그래피(High Performance Liquid Chromatography: HPLC)를 이용하여 분석하였다. 분석에 사용된 GC는 휴렛팩커드 5890 시리즈 II(Hewlett Packard 5890 Series II)이고, HPLC는 스펙트라시스템(SpectraSystem) P2000이다.

【표 1】

구분	알콜의 합성수율(%)	키랄 아세테이트의 합성수율(%)	광학순도(e.e.%)
실시예 1	1	95	97
실시예 2	0	81	99
실시예 3	2	92	99
실시예 4	0	85	99
실시예 5	3	86	99
실시예 11	2	96	98
실시예 12	2	94	99
실시예 13	2	98	99
실시예 14	0	94	97
실시예 15	0	100	99
실시예 16	0	98	99
실시예 17	0	95	95

상기 표 1로부터 알 수 있는 바와 같이, 실시예 1-5, 11-17에 따라 수소화물 반응과 라세미화반응을 동시에 진행시키는 루테늄 착물과 알콜의 에스테르화 반응을 진행시키는 리파아제를 적절히 조화시켜 케톤으로부터 키랄 에스테르를 1단계 반응으로 제조할 수 있었고, 이렇게 얻어진 키랄 에스테르의 광학순도가 우수하였다. 또한, 비반응 알콜의 함량을 5% 이하으로 키랄 에스테르의 합성수율도 우수하다는 것을 확인할 수 있었다.

【발명의 효과】

본 발명에 따르면, 케톤으로부터 1단계 반응을 거쳐 간단한 방법으로 광학순도 특성이 우수한 키랄 에스테르를 높은 합성수율로 얻을 수 있다.

【특허청구범위】

【청구항 1】

다음 화학식 1의 제[illegible].

상기 제[illegible] 디엔[illegible] 화합물[illegible] [illegible] 및, 그 상기 디엔[illegible] [illegible] [illegible] 반응[illegible] 화학식 1 내지 2의 [illegible] 제조함.

상기 디엔[illegible] 화합물은 [illegible] [illegible] 선택적으로 [illegible]

[illegible].

상기 [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]

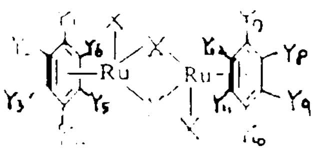
[illegible].

상기 [illegible] [illegible] [illegible] [illegible] [illegible] 및

[illegible], 하여서 다음 화학식 1의 [illegible] 제조함을 특징으로 하는

이량 [illegible]의 제조방법.

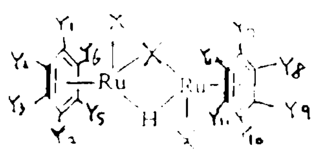
[화학식 1]



상기식중, Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, Y_{12}는 서로에 관계없이 단일결합을 나타내거나, 수소 또는 탄소수 1 내지 5의 알킬기를 나타내고

X는 Br, Cl 또는 I이다.

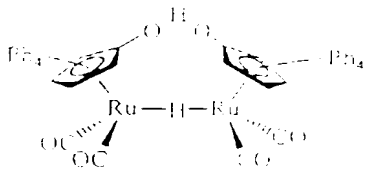
[화학식 2]



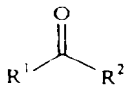
상기식중, Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, Y_{12}는 서로에 관계없이 단일결합을 나타내거나, 수소 또는 탄소수 1 내지 5의 알킬기를 나타내고

식 1a, 식 1b, 식 1c 또는 식 1d로 표시되는 화합물.

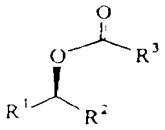
[화학식 1]



[화학식 II]



[화학식 100]

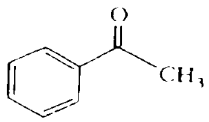


상기 화학식 1 및 화학식 100에서 R^1, R^2 및 R^3는 서로 독립적으로 비치환된 또는 치환된 알킬기, 비치환된 또는 치환된 아릴기, 비치환된 또는 치환된 사이클로알킬기 이루어진 군으로부터 선택되고, 상기에 따라서 R^1과 R^2, R^2과 R^3, R^3과 R^1 서로 연결된 형태일 수 있다.

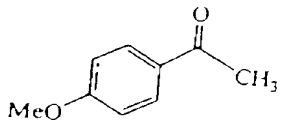
【실시예 2】

제 1 항에 있어서, 상기 제조는 다음 화학식 1a - 1g중에서 선택된 화합물을 제조하는 방법.

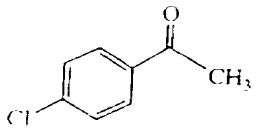
[화학식 1a]



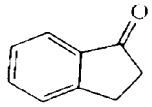
[화학식 1b]



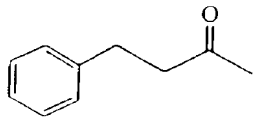
[화학식 1c]



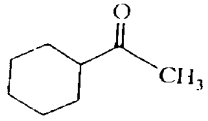
[화학식 1d]



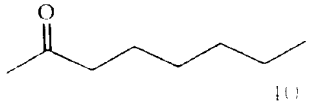
[화학식 1e]



[화학식 1f]



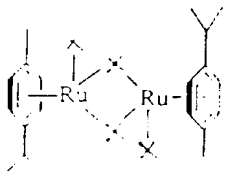
[화학식 1g]



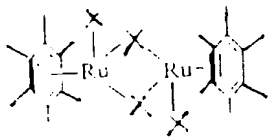
【청구항 3】

제 1 항에 있어서, 상기 유비퀴논 화합물이 하기 화학식 5-10로 표시되는 화합물 중에서 선택되는 것을 특징으로 하는 방법.

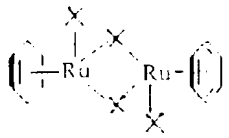
[화학식 5]



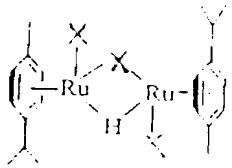
[화학식 6]



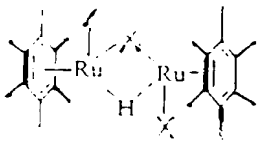
[화학식 7]



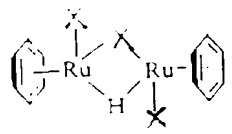
[화학식 8]



[화학식 9]



[화학식 10]



상기식중, X는 Br, Cl 또는 I이다.

【청구항 4】

제 1 항에 있어서, 상기 화학식 1 내지 3의 화합물에서, X가 Cl인 것을 특징으로 하는 방법.

【청구항 5】

제 1 항에 있어서, 상기 리파아제가 슈도모나스 세파시아스 리파아제(*Pseudomonas cepacias* lipase), 캔디다 안타르티카 리파아제(*candida antarctica* component B lipase)로 이루어진 군으로부터 선택되는 것을 특징으로 하는 방법.

【청구항 6】

제 1 항에 있어서, 상기 아실 도너가 아릴 에스테르인 것을 특징으로 하는 방법.

【청구항 7】

제 6 항에 있어서, 상기 아릴 에스테르가 p-할로페닐 아세테이트 및 알케닐 아세테이트로 이루어진 군으로부터 선택되는 것을 특징으로 하는 방법.

【청구항 8】

제 1 항에 있어서, 상기 하이드라이드 도너가 2,6-디메틸헵탄-4-올,

청소 및 부대상품을 내장하여 구성하되 장바퀴는 것을 특징으로 하는 방법.

【청구항 9】

제 1 항에 있어서, 상기 부대품 차종의 장량이 제품을 기준으로 하여 그에 대응하는 것을 특징으로 하는 방법.

【]

【]

[illegible]

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(74) Agent: **HUH, Sang, Hoon**; Hyecheon Building, 13th Floor, 831, Yeoksam-dong, Kangnam-ku, Seoul 135-792 (KR).

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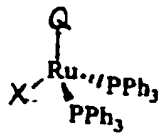
[Continued on next page]

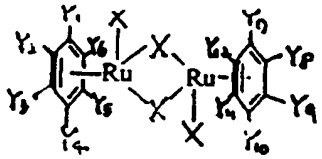
(54) Title: PREPARING METHOD OF CHIRAL ESTER



(1)

(a)

(b)



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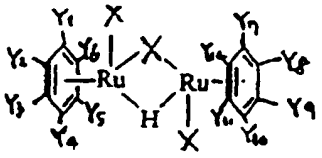
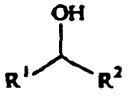


(3)



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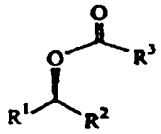

(100)

(57) Abstract: The present invention is to provide a process for preparing a chiral ester expressed in formula (100) by reacting; a racemic alochol of formula (4); a ruthenium complex selected from the group consisting of compounds 1,2 and 3 expressed in formulas (1),(2), and (3) to activate racemization of said racemic alchol; a lipase to acylate one enantiomer selectively from said racemic alcohol; and an acyl donor compound to supply acyl group to said lipase, formula (1) wherein Q is (a) or (b); and X is Br, Cl or I; formula (2) wherein Y_1,Y_2,Y_3,Y_4,Y_5,Y_6,Y_7,Y_8,Y_9,Y_{10},Y_{11} and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; formula (3) wherein Y_1,Y_2,Y_3,Y_4,Y_5,Y_6,Y_7,Y_8,Y_9,Y_{10},Y_{11}, and Y_{12}, are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; and formulae wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R' and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

WO 01/28970 A1

DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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PREPARING METHOD OF CHIRAL ESTER

BACKGROUND OF THE INVENTION

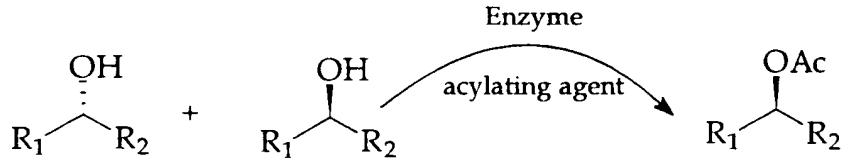
Field of the Invention

The present invention relates to a method for preparing a chiral ester and more particularly, the method for preparing an optically pure chiral ester from a racemic alcohol at a high yield.

Recently, studies for using a metal or an enzyme as a catalyst have been increased in asymmetric syntheses. It has been widely known to use an enzyme as a catalyst for kinetic resolution of a racemic mixture in organic syntheses. A variety of effective methods for hydrolysis of an ester and acylation of an alcohol in the presence of lipase as a catalyst has been reported.

Kinetic resolution is the fact that the two enantiomers react at different rates with a chiral addend. An effective kinetic resolution is the enantioselective conversion from a racemic mixture to an optically pure product as shown in scheme 1, leaving the other enantiomer in a reaction medium.

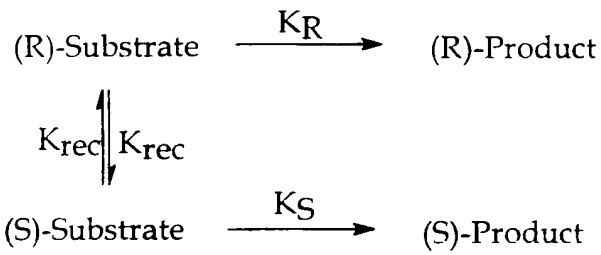
Scheme 1



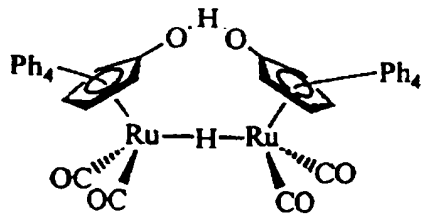
It is well known to prepare a chiral ester from a racemic alcohol by kinetic resolution using esterase. It is possible to obtain an optically pure ester but a maximum yield of this reaction is limited to 50% as shown in scheme 1. Therefore, dynamic kinetic resolution performing kinetic resolution and racemization of an alcohol simultaneously is introduced to resolve such

problems (scheme 2).

Scheme 2



The well-known example of a dynamic kinetic resolution is the reaction by using ruthenium complex expressed in the following structure and lipase (Novozym 435) [B. A. Persson, A. L. E. Larsson, M. L. Ray, and J. E. Backvall, *J. Am. Chem. Soc.* 1999, **121**, 1645].



Because racemization of a starting material is performed simultaneously with kinetic resolution, the effectiveness of the starting material is very high and thus, yield of obtaining (R) or (S) enantiomer is theoretically 100%. However, even if the optical purity of a chiral ester obtained by dynamic kinetic resolution is 99 e. e.%, 12 to 40% of ketone as a by-product is produced.

SUMMERY OF THE INVENTION

Therefore, an object of the present invention is to provide a process for preparing an optically pure chiral ester from a racemic alcohol by dynamic kinetic resolution with minimum production of a ketone.

Detailed Description of the Invention

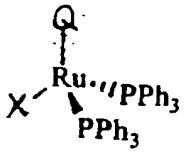
A process for preparing a chiral ester of the present invention is characterized by reacting:

a racemic alcohol;

a ruthenium complex selected from the group consisting of compounds 1, 2 and 3 expressed in formulas 1 to 3 to activate racemization of said racemic alcohol;

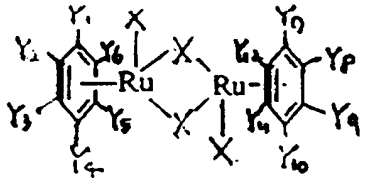
a lipase to acylate selectively one of enantiomers of said racemic alcohol; and

an acyl donor group to supply acyl group to said lipase,



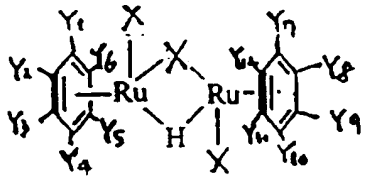
(1)

wherein Q is  or  ; and X is Br, Cl or I;



(2)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;

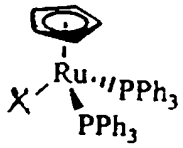


(3)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a

hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I.

Said ruthenium complex is selected from the group consisting of the compounds 5 to 12 expressed in the following formulas 5 to 12,



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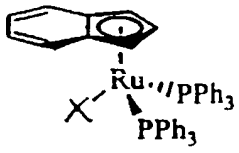

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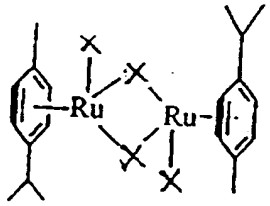

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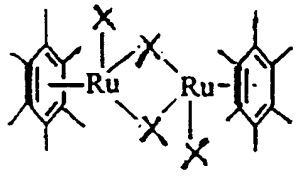

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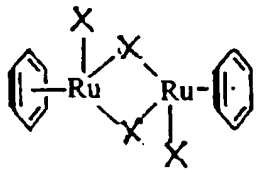

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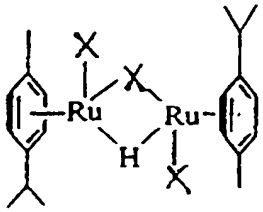

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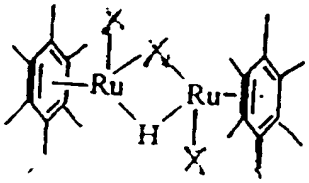

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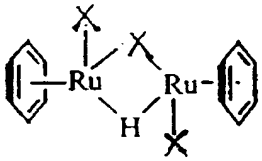


(12)

wherein X is Cl, Br or I, the most preferably Cl.

Preferred content of ruthenium complex is 0.1 to 5 mol%, relative to a racemic alcohol. If the content is more than 5 mol%, cost becomes expensive. On the other hand, if it is less than 0.1 mol%, the rate of the reaction becomes too slow.

A method for preparing a chiral ester from a racemic alcohol by dynamic kinetic resolution is described in detail as set forth hereunder.

A mixture of a racemic alcohol, ruthenium complex selected from compounds 1, 2 and 3, lipase and an acyl donor compound is reacted in a solvent in the presence of a base shown in Scheme 3,

Scheme 3

(4) (100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

A reaction condition varies with a structure of ruthenium complex. When the ruthenium complex of formula 6 is used, an oxygen gas is required essentially in the reaction and it is performed at a temperature of 40 to 60℃. Said oxygen gas reacts with phosphine, which is a ligand bonded with ruthenium, to convert to phosphine oxide. When the ruthenium complex of formula 7 is used, the reaction is performed at a temperature of 20 to 40℃. When the ruthenium complex of formula 10 is used, the reaction is performed at a temperature of 20 to 40℃. A base is also required to remove acid generated during the reaction. Said base includes triethylamine or diisopropylethyl amine but it is not limited to these examples.

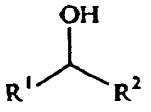
The ruthenium complex of formula 7 is commercially available and is converted to the ruthenium complex of formula 10 in alcohol/base condition. Therefore, results from the ruthenium complex of formula 7 and the ruthenium complex of formula 10 are almost same.

A mechanism of a reaction of a racemic alcohol, ruthenium complex selected from compounds 1, 2 and 3, lipase and an acyl donor compound is described in detail hereunder.

An acyl group supplied from the acyl donor compound is reacted with lipase and this lipase is further reacted with one enantiomer of a racemic alcohol selectively to produce a chiral ester. The other enantiomer is racemized by reacting with ruthenium complex. And further one enantiomer from this racemic alcohol is acylated selectively by lipase and this reaction is repeated to produce optically pure chiral ester with preventing generation of ketone which is a by-product in conventional dynamic kinetic resolution.

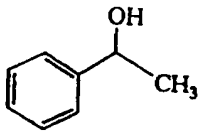
Reaction solvent is not limited but it is preferred to use methylene chloride, toluene, benzene, or hexane because a solvent commonly affects production yield in enzymatic catalysis reaction. An amount of said solvent is used to be 0.2 to 0.3 M concentration of a racemic alcohol.

Said racemic alcohol is generally expressed in the formula 4. It is not limited but examples of the present invention are the following compounds 4a, 4b, 4c, 4d, 4e or 4f,

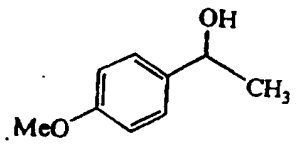


(4)

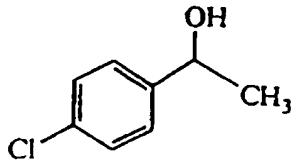
wherein R^1 and R^2 are the same as defined above.



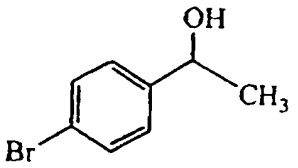
(4a)



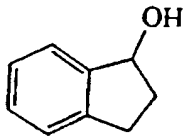
(4b)



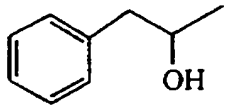
(4c)



(4d)



(4e)



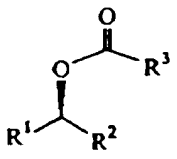
(4f)

Said lipase, which is esterase, acylates one enantiomer from a racemic alcohol selectively to a chiral ester. Examples of lipase are *Pseudomonas cepacias* lipase and *Candida antarctica* lipase and more particulary, *Candida antarctica* component B lipase supported on acrylic resin (Novozym 435, Novo company) or *Pseudomonas cepacias* lipase supported on ceramic particle (lipase PS-C, Amano company). An amount of said lipase is in the range of 10 to 60mg, preferably 30 mg, relative to 1 mmol of an alcohol in Novozym 435 case, and is in the range of 50 to 320 mg, preferably 160 mg, relative to 1 mmol of an alcohol in lipase PS-C case.

Said acyl donor supplies an acyl group to a lipase and acts to move a reaction balance to an acylated product in the presence of a lipase. Preferred acyl donor is aryl ester or alkenyl acetate, the most preferably aryl ester such as

p-chlorophenyl acetate having electron withdrawing group. An example of alkenyl acetate is isoprophenyl acetate. Such acyl donor compounds are preferred to use because they have an appropriate reactivity without inhibiting racemization. A preferred amount of said acyl donor compound is 2 to 4 equivalents to 1 equivalent of racemic alcohol. If the amount is more than 4 equivalents to 1 equivalent of racemic alcohol, it is difficult to isolate after a reaction. On the other hand, if it is less than 2 equivalents to 1 equivalent of racemic alcohol, the rate of acylation becomes too slow.

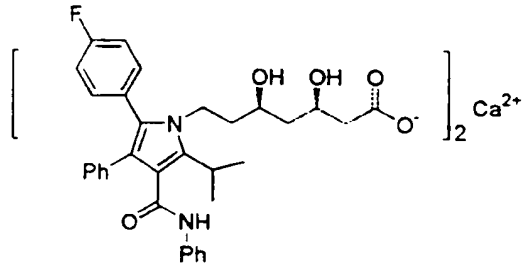
A chiral ester expressed in formula 100 is obtained by reacting a racemic alcohol, a ruthenium complex, a lipase, and an acyl donor compound,



(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

The chiral ester of formula 100 of the present invention can be used as a synthetic intermediate for preparing various chiral compounds, chiral pharmaceutical drugs or chiral agrochemicals and more particularly, used as an essential intermediate for preparing Atorvastatin expressed in formula 101 which is a useful drug for treatment for hyperlipemia, L-Carnitine expressed in formula 102 which is as an additive used in food and drugs, and Agenerase expressed in formula 103 which is an essential intermediate of AIDS drug.



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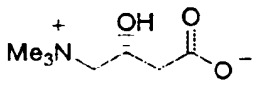

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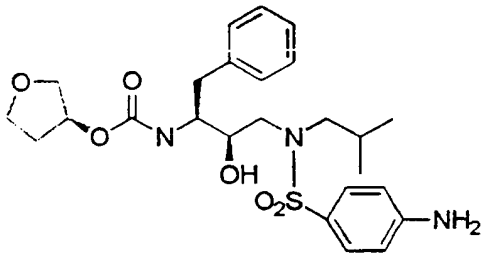
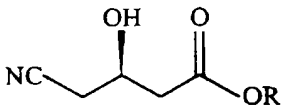


(103)

Especially, a chiral compound of formula 100a which is one of the compounds of the present invention is a key intermediate for preparing Atorvastatin of formula 101 disclosed in US Patent No. 5,908,953,



(100a)

wherein R is a low alkyl group.

The process for preparing a chiral ester of formula 100 of the present invention provides minimum production of by-products such as unreacted alcohol residue up to less than 10% and maximum production of product up to 98% having a high optical purity of 99% or more. Because optical purity is the most important factor in preparing chiral compounds for food and pharmaceutical drugs, the chiral ester of the present invention can be used as a useful starting material in various fields, especially fine chemical field.

The following examples are intended to be illustrative of the present invention and should not be construed as limiting the scope of this invention defined by the appended claims.

Example 1

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.75mmol), ruthenium complex of formula 6(0.0130mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 2.0ml of dichloromethane to give a redish brown suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition. Oxygen(0.0130mmol) was injected with syringe in the reaction suspension and then it was heated at 60℃ for 43 hours.

Examples 2-6

The product, a chiral ester, was prepared by the same procedure of Example 1 except to use racemic alcohol of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Example 7

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.25mmol), ruthenium complex of formula 7(0.0130mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 1.2ml of methylene chloride to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition and then it was heated at 40℃ for 44 hours.

Examples 8-12

The product, chiral ester, was prepared by the same procedure of Example 6 except to use racemic alcohols of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Example 13

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.25mmol), ruthenium complex of formula 10(0.0100mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 1.2ml of methylene chloride to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition and then it was heated at 40℃ for 44 hours.

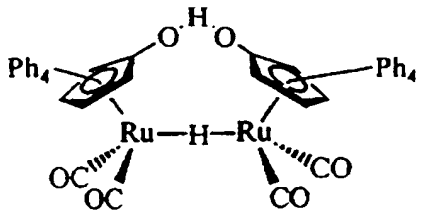
Examples 14-18

The product, chiral ester, was prepared by the same procedure of Example 11 except to use a racemic alcohol of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Comparative Example 1

A racemic alcohol of formula 4a(2mmol), ruthenium complex expressed in the following structure below(0.04mmol), 60mg of Novozym 435, and *p*-chlorophenyl acetate(6mmol) were mixed in 5ml of toluene to give a dark redish suspension.

The reaction suspension was heated at 70℃ for 46 hours under argon gas.



Comparative Examples 2-5

The product, a chiral ester, was prepared by the same procedure of Comparative Example 1 except to use racemic alcohols of formulas 4b, 4d, and 4e and octan-2-ol instead of a racemic alcohol of formula 4a.

Yield, optical purity, and formation of ketone of each reaction of Examples 1-15 and Comparative Examples 1-5 were determined and tabled in Table 1. Said yield was analyzed by ^{1}H-NMR spectrum, and said optical purity was determined by high performance liquid chromatography. Said ^{1}H-NMR spectrum was taken by using Bruker AM 300 and said high performance liquid chromatography was SpectraSystem P2000.

Table 1

Section	Formation of ketone (%)	Yield (%)	Optical purity (e.e.%)
Example 1	0	85	96
Example 2	0	82	99
Example 3	0	98	99
Example 4	0	91	95
Example 5	0	85	97
Example 6	0	92	96
Example 7	8	90	94
Example 8	10	90	99
Example 9	8	90	99

Example 10	8	92	99
Example 11	8	83	99
Example 12	7	91	98
Example 13	5	95	94
Example 14	7	93	99
Example 15	5	93	97
Example 16	4	96	99
Example 17	4	85	99
Example 18	4	95	99
Comp. Example 1	20	Below 80	-
Comp. Example 2	40	Below 60	-
Comp. Example 3	22	Below 78	-
Comp. Example 4	23	Below 77	-
Comp. Example 5	20	Below 80	-

As shown in Table 1, the amount of a ketone formed as a by-product in Comparative Examples 1 to 5 is in the range of 20 to 40% while that in Examples 1 to 18 is less than 10%. Therefore, the yield of the final product, a chiral ester, prepared by Examples 1 to 18 is much more improved.

As a result, it is proved that the present invention provides a process for preparing an optically pure chiral ester from a racemic alcohol with minimizing the formation of ketone at a high yield in the presence of catalysts which are ruthenium complex selected from formulas 1, 2, and 3, and lipase.

CLAIMS

What is claimed is :

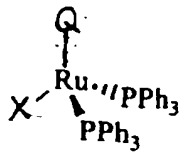
1. A process for preparing a chiral ester expressed in formula 100 by reacting;

a racemic alcohol of formula 4;

a ruthenium complex selected from the group consisting of compounds 1, 2, and 3 expressed in formulas 1, 2, and 3 to activate racemization of said racemic alcohol;

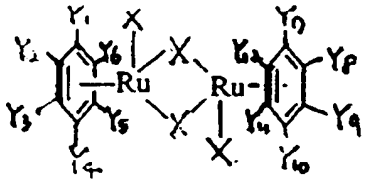
a lipase to acylate one enantiomer selectively from said racemic alcohol; and

an acyl donor compound to supply acyl group to said lipase,



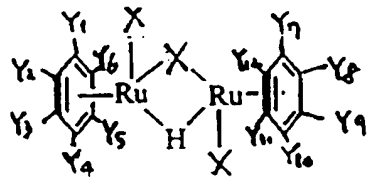
(1)

wherein Q is  or  ; and X is Br, Cl or I;



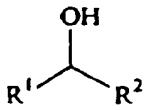
(2)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;



(3)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I; and



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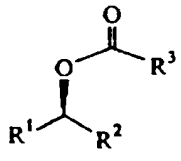
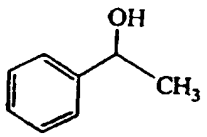


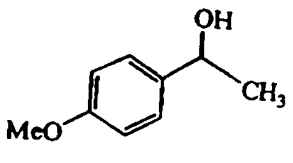
(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

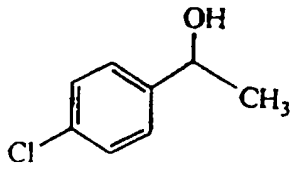
2. The process for preparing a chiral ester according to claim 1, wherein said racemic alcohol is selected from the group consisting of the compounds 4a, 4b, 4c, 4d, 4e and 4f.



(4a)



(4b)



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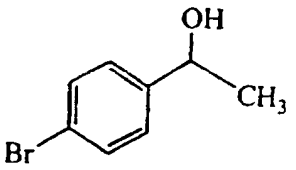
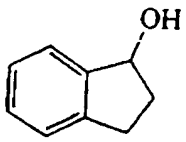
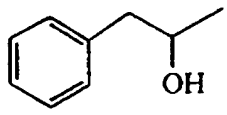


(4d)



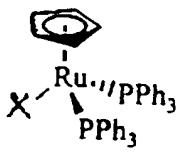
(4e)



(4f)

3. The process for preparing a chiral ester according to claim 1, wherein said lipase is selected from the group consisting of *Pseudomonas cepacias* lipase and *Candida antarctica* lipase.

4. The process for preparing a chiral ester according to claim 1, wherein said ruthenium complex is selected from the group consisting of compounds 5, 6, 7, 8, 9, 10, 11 and 12,



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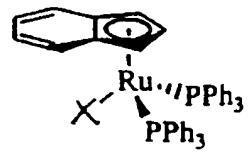

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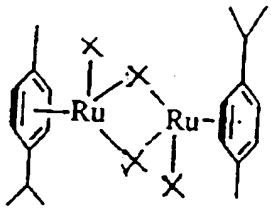

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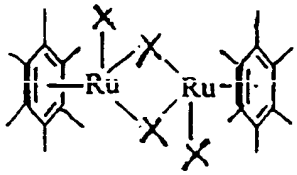

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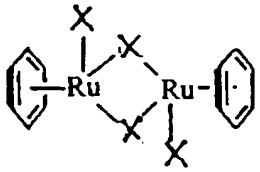

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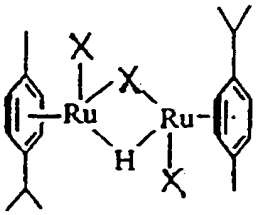

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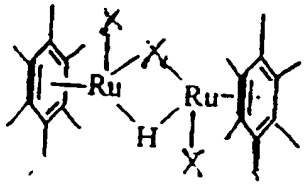

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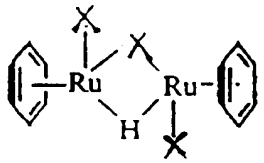

(12)

wherein X is Cl, Br or I, the most preferably Cl.

5. The process for preparing a chiral ester according to claim 3, wherein X is Cl.

6. The process for preparing a chiral ester according to claim 1, wherein said reaction requires use of oxygen gas.

7. The process for preparing a chiral ester according to claim 1, wherein a content of said ruthenium complex or its derivatives is in the range of 0.1 to 5mol% to said racemic alcohol.

8. The process for preparing a chiral ester according to claim 1, wherein said acyl donor compound is aryl ester.

9. The process for preparing a chiral ester according to claim 7, wherein said aryl ester is selected from the group consisting of *p*-chlorophenyl acetate and alkenyl acetate.

INTERNATIONAL ARCH REPORT

/national application No.
PCT/KR00/01170

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07C 67/00, C12P 7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)
C07C, C12P

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)
STN(REGISTRY, CAPLUS)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T,A	Novel synthetic routes to several new, differentially substituted ruthenium tris(4,4'-disubstituted-2,2-bipyridine) complexes, Dusan Hsek et al, page 308-316, American Chemical Society (2000), 39(2) see the scheme 1 and table 1	1-9
T,A	Catalytic asymmetric and chemoselective aerobic oxidation : kinetic resolution of sec-alcohols, Masutani K. et al, page 5119-5123, Tetrahedron letters (2000) 41(26) see the page 5120(reaction, scheme) and table 1	1-9
T,A	synthesis of ruthenium complexes with planar-chiral cyclopentadienyl-pyridine or -phosphine bidentate ligands, Noriko Dodo et al, page 35-41, Dalton (2000) 1, Royal Society of chemistry see the scheme 2 and 5	1-9
A	EP-A2-375417 see the whole document	1-9
P,A	EP-A1-992481 see the whole document	1-9
A	Ruthenium(2)-catalyzed asymmetric transfer hydorgenation of ketones using a formic acid-triethylamine mixture, Fujii, Akio et al, page 2521-2, American Chemical Society (1996),	1-9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 FEBRUARY 2001 (09.02.2001)	12 FEBRUARY 2001 (12.02.2001)

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Telephone No. 82-42-481-5536

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR00/01170

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2-375417	1990.6.27	JP-A2-02-169555	1990.6.29
EP-A1-992481	2000.4.12	DE-A1-1998-5517	2000.4.6
		JP-A2-2000-119217	2000.4.25

----------End of documents----------

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(74) Agent: **HUH, Sang, Hoon**; 13th Fl. Hyecheon Bldg, 831, Yeoksam-dong, Kangnam-ku, Seoul 135-792 (KR).

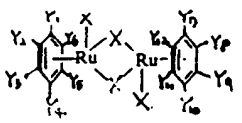
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR PREPARING CHIRAL ESTER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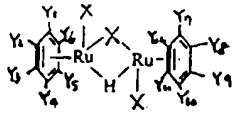
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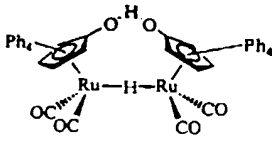
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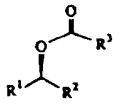
(100)

(57) Abstract: The present invention relates to a process for preparing a chiral ester expressed in formula (100) by mixing and reacting: a ketone of formula (4); a ruthenium complex selected from the group consisting of compounds (1, 2 and 3) expressed in formula (1) to (3) to activate hydrogenation of said ketone to a racemic alcohol and racemization of said racemic alcohol; a lipase to acylate selectively one of enantiomers of said racemic alcohol; a hydride donor group to supply a hydride group to said ruthenium complex; and an acyl donor group to supply acyl group to said lipase. In formula (1) wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independentlya hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I. In formula (2) wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6 Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl, or I. In formulae (3), (4), and (100) wherein R^1, R^2, and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cyclyoalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

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METHOD FOR PREPARING CHIRAL ESTER

BACKGROUND OF THE INVENTION

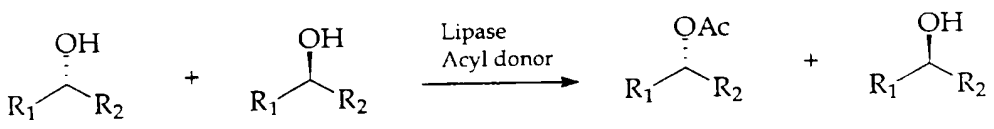
Field of the Invention

The present invention relates to a method for preparing a chiral ester and more particularly, the method for preparing an optically pure chiral ester from a ketone at a high yield by using an enzyme and a metallic catalyst.

It is one of important aims to convert a racemic mixture to an optically pure compound enantioselectively in organic synthesis. Recently, studies for using a metal or an enzyme as a catalyst have been increased in asymmetric syntheses. It has been widely known to use an enzyme as a catalyst for kinetic resolution of a racemic mixture in organic syntheses. A variety of effective methods for hydrolyses of esters and acylations of alcohols in the presence of lipase as a catalyst have been reported.

Kinetic resolution is the fact that the two enantiomers react at different rates with a chiral addend. An effective kinetic resolution is the enantioselective conversion from the racemic mixture to an optically pure product (scheme 1), leaving the other enantiomer in the reaction mixture.

Scheme 1



Conventional methods for preparing a chiral ester from a ketone such as asymmetric hydrogenation of an enol ester converted from a ketone, or esterification of a chrial alcohol prepared by asymmetric hydrogenation of a

ketone require at least more than two step syntheses from a ketone to an enol ester. These methods are relatively long and complicate.

SUMMARY OF THE INVENTION

Therefore, an object of the present invention is to provide a simple process for preparing an optically pure chiral ester at a high yield to resolve the above problems.

Detailed Description of the Invention

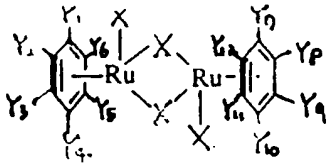
A process for preparing a chiral ester of the present invention is characterized by mixing and reacting: a ketone;

a ruthenium complex selected from the group consisting of compounds 1, 2 and 3 expressed in formulas 1 to 3 to activate hydrogenation of said ketone to a racemic alcohol and racemization of said racemic alcohol;

a lipase to acylate selectively one of enantiomers of said racemic alcohol;

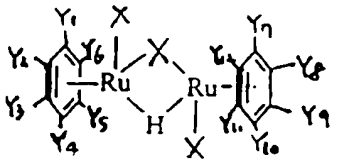
a hydride donor group to supply a hydride group to said ruthenium complex; and

an acyl donor group to supply acyl group to said lipase,



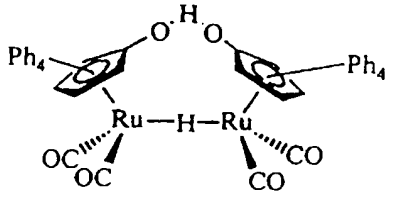
(1)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;



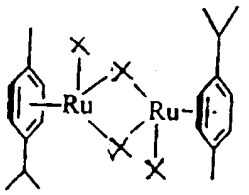
(2)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;

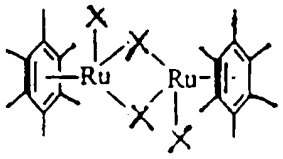


(3)

Said ruthenium complex is selected from the group consisting of the compounds 5 to 10 expressed in the following formulas 5 to 10,



(5)



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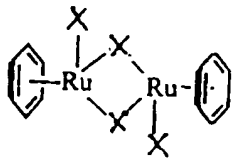

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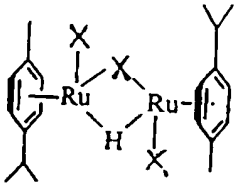

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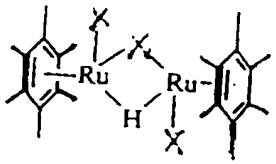

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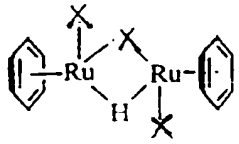


(10)

wherein X is Cl, Br or I, the most preferably Cl.

A method for preparing a chiral ester from a ketone through one-step synthesis is described in detail as set forth hereunder.

A mixture of a ruthenium complex selected from the group consisting of formulas 1 to 3, a lipase, a hydride donor, an acyl donor, and a ketone is reacted in an appropriate solvent in the presence of a base as shown in Scheme 2. The reaction condition can be varied with a structure of ruthenium complex. For example, when the ruthenium complex of formula 5 is used, the reaction is performed at a temperature of 40 to 50℃. When the ruthenium complex of formula 8 is used, the reaction requires 40 to 50℃ of a reaction temperature. When the ruthenium complex of formula 3 is used, the reaction requires 70 to 80℃ of a reaction temperature. The ruthenium complex of formula 5 is commercially available and can be converted to the ruthenium complex of formula 8 in alcohol/amine base condition. Therefore, results from the ruthenium complex of formula 5 and the ruthenium complex of formula 8 are almost same. A content of said ruthenium complex is preferred to use 0.1 to 5 mol%, relative to a ketone. If the content is more than 5 mol%, cost becomes expensive. On the other hand, if it is less than 0.1 mol%, the rate of the reaction becomes too slow.

Scheme 2

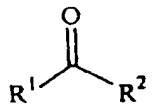
(4) (100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as halogen atom and a cyano group.

Said ruthenium complex activates hydrogenation reaction of a ketone to a racemic alcohol by acting as a catalyst to transfer a hydrogen atom and further activates racemization of obtained racemic alcohol.

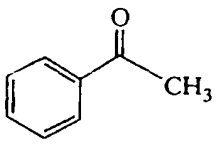
Said lipase, which is esterase, acylates one enantiomer from a racemic alcohol selectively to a chiral ester. Examples of lipase are *Pseudomonas cepacias* lipase and *Candida antarctica* lipase and more particulary, *Candida antarctica* component B lipase supported on acrylic resin (Novozym 435, Novo company) or *Pseudomonas cepacias* lipase supported on ceramic particle (lipase PS-C, Amano company), the most preferably *Candida antarctica* component B lipase supported on acrylic resin for heat resistance, reactivity, optical purity and the like. An amount of said lipase is in the range of 10 to 60mg, preferably 30 mg, relative to 1 mmol of a ketone in Novozym 435 case, and is in the range of 40 to 240 mg, preferably 80 mg, relative to 1 mmol of ketone in lipase PS-C case.

Said ketone is generally expressed in the formula 4. It is not limited but examples of the present invention are compounds 4a, 4b, 4c, 4d, 4e, 4f or 4g,



(4)

wherein R^1 and R^2 are the same as defined above.



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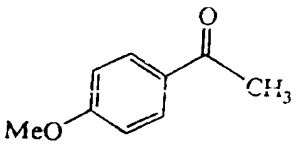

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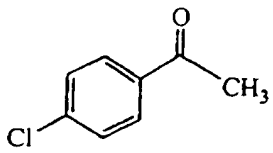

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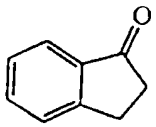

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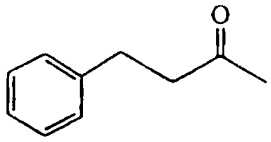

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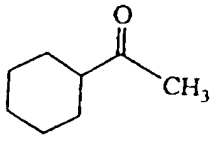

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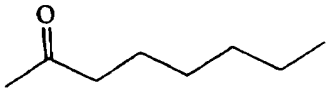


(4g)

Said acyl donor supplies an acyl group to a lipase and acts to move a reaction balance to an acylated product in the presence of lipase catalyst. Preferred acyl donor is aryl ester or alkenyl acetate, the most preferably aryl ester such as *p*-chlorophenyl acetate having electron withdrawing group. An example of alkenyl acetate is isoprophenyl acetate. Such acyl donor compounds are preferred to use because they have an appropriate reactivity without inhibiting racemization. A preferred amount of said acyl donor compound is 2 to 4 equivalents to 1 equivalent of a ketone. If the amount is more than 4 equivalents to 1 equivalent of a ketone, it is difficult to isolate after reaction. On the other hand, if it is less than 2 equivalents to 1 equivalent of a ketone, the rate of acylation becomes too slow.

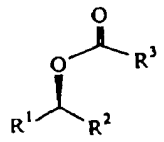
A hydride donor supplies a hydride to ruthenium complex. Examples of said hydride donor are 2,6-dimethylheptan-4-ol, hydrogen, and formic acid. Preferred amount of said hydride donor is 1 to 2 equivalents to 1 equivalent of ketone. If the content deviates from the range, it inhibits racemization reaction.

A base is also required to remove acid generated during the reaction. Said base includes triethylamine or diisopropylethyl amine and preferred amount to use is in the range of 1 to 2 equivalents to 1 equivalent to ketone.

Reaction solvent is not limited but it is preferred to use methylene chloride, toluene, benzene, or hexane because a solvent commonly affects production yield in enzymatic catalysis reaction. An amount of said solvent is used to be 0.2 to 0.3 M concentration of a ketone.

A chiral ester expressed in formula 100 is obtained by reacting a ketone, a ruthenium complex, a lipase, and an acyl donor compound in the presence of

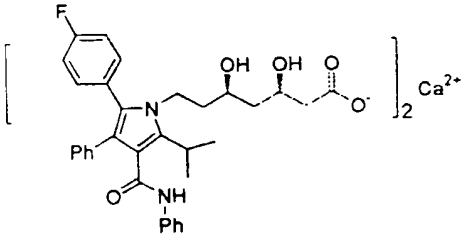
hydride donor,



(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

The chiral ester of formula 100 of the present invention can be used as a synthetic intermediate for preparing various chiral compounds, chiral pharmaceutical drugs or chiral agrochemicals and more particularly, used as an essential intermediate for preparing Atorvastatin expressed in formula 101 which is a useful drug for treatment for hyperlipemia, L-Carnitine expressed in formula 102 which is as an additive used in food and drugs, and Agenerase expressed in formula 103 which is an essential intermediate of AIDS drug.



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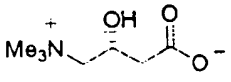

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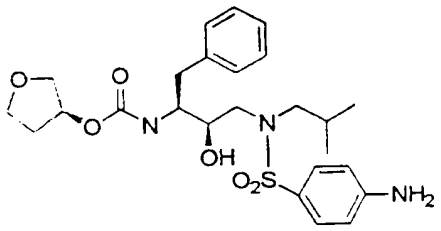
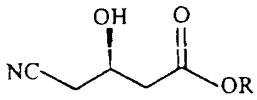


(103)

Especially, a chiral compound of formula 100a which is one of the compounds of the present invention is a key intermediate for preparing Atorvastatin of formula 101 disclosed in US Patent No. 5,908,953,



(100a)

wherein R is a low alkyl group.

The process for preparing a chiral ester of formula 100 of the present invention provides minimum production of by-products such as unreacted alcohol residue up to less than 5% and maximum production of product up to 100% having a high optical purity of 99% or more. Because optical purity is the most important factor in preparing chiral compounds for food and pharmaceutical drugs, the chiral ester of the present invention can be used as a useful starting material in various fields, especially fine chemical field.

The following examples are intended to be illustrative of the present invention and should not be construed as limiting the scope of this invention defined by the appended claims.

Example 1

A ketone of formula 4a(0.25mmol), triethylamine(0.75mmol), ruthenium complex of formula 5(0.0130mmol), where X is Cl, 2,6-dimethylheptan-4-ol(0.38mmol), and 20mg of lipase PS-C(Amano Company) were added to 2.0ml

of methylene chloride. The reaction mixture was stirred for 5 min at room temperature and *p*-chlorophenyl acetate(0.75mmol) was added thereto to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing an oxygen under the vacuum condition and then the suspension was heated at 50℃ for 78 hours.

Examples 2 to 5

The product, a chiral ester, was prepared by the same procedure of Example 1 except to use ketone of formulas 4b-4e instead of a ketone of formula 4a.

Example 6

The product, a chiral ester, was prepared by the same procedure of Example 1 except to use ruthenium complex of formula 8, where X is Cl, instead of the ruthenium complex of formula 5, where X is Cl.

Examples 7 to 10

The product, a chiral ester, was prepared by the same procedure of Example 6 except to use ketone of formulas 4b-4e instead of a ketone of formula 4a.

Example 11

A ketone of formula 4a(0.25mmol), ruthenium complex of formula 3(0.050mmol), 2,6-dimethylheptan-4-ol(0.38mmol), 7.5mg of Nozyme 435 and *p*-chlorophenyl acetate(0.75mmol) were added to 0.8ml of toluene to give a yellow suspension.

Argon gas was purged into the reaction suspension, after removing an oxygen under the vacuum condition and then the suspension was heated at 70℃ for 44 hours.

Examples 12 to 17

The product, a chiral ester, was prepared by the same procedure of Example 11 except to use ketone of formulas 4b-4g instead of a ketone of formula 4a.

In examples 1 to 5 and examples 11 to 17 to prepare chiral esters, formation of an alcohol as a by-product, yield of chiral acetates, and optical purity were determined and tabled in Table 1. Said yields of an alcohol and chiral acetate were analyzed by gas chromatography, and said optical purity was determined by high performance liquid chromatography. Said gas chromatography used was Hewlett Packard 5890 Series II and said high performance liquid chromatography was SpectraSystem P2000.

Table 1

Section	Formation of alcohol (%)	Yield (%)	Optical purity (e.e.%)
Example 1	1	93	97
Example 2	0	81	99
Example 3	2	92	99
Example 4	0	73	99
Example 5	5	86	99
Example 11	2	96	98
Example 12	2	94	99

Example 13	2	98	99
Example 14	0	94	97
Example 15	0	100	99
Example 16	0	98	99
Example 17	0	95	95

As shown in Table 1, examples 1 to 5 and examples 11 to 17 proved that the present invention provides one-step synthesis for preparing an optically pure chiral ester form a ketone by controlling ruthenium complex to activate racemization and hydrogen transfer and lipase to activate esterification. Further, it provides high formation of the product, chiral ester, having less than 5% of unreacted alcohols.

CLAIMS

What is claimed is:

1. A process for preparing a chiral ester expressed in formula 100 of the present invention is characterized by mixing and reacting:

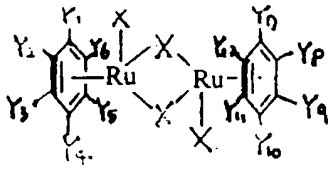
a ketone expressed in formula 4;

a ruthenium complex selected from the group consisting of compounds 1, 2 and 3 expressed in formulas 1 to 3 to activate hydrogenation of said ketone to a racemic alcohol and racemization of said racemic alcohol;

a lipase to acylate selectively one of enantiomers of said racemic alcohol;

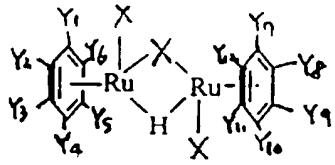
a hydride donor group to supply hydride group to said ruthenium complex; and

an acyl donor group to supply acyl group to said lipase,



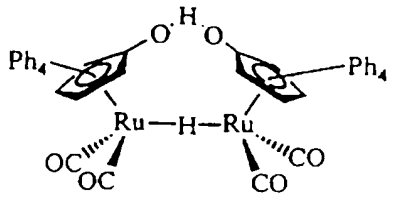
(1)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;



(2)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;



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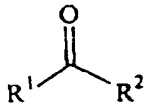

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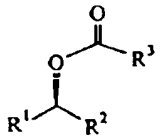
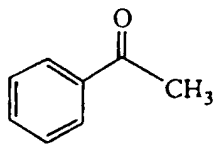


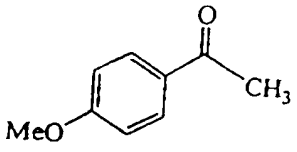
(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

2. The process for preparing a chiral ester according to claim 1, wherein said ketone is selected from the group consisting of the compounds 4a, 4b, 4c, 4d, 4e, 4f and 4g of formulas 4a to 4g.



(4a)



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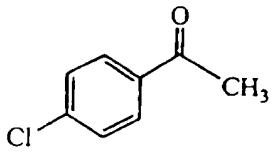

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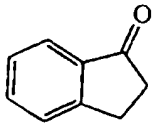

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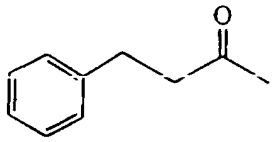

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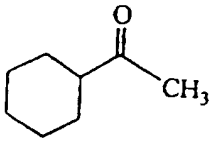

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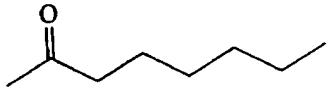
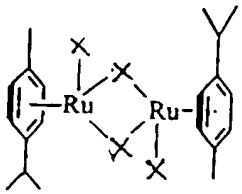


(4g)

3. The process for preparing a chiral ester according to claim 1, wherein said ruthenium complex is selected from the group consisting of compounds 5, 6, 7, 8, 9, and 10,



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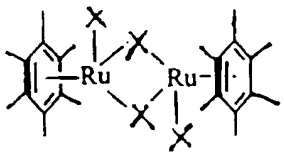

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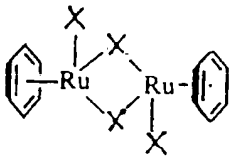

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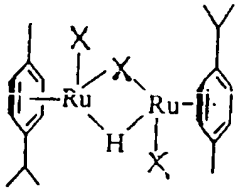

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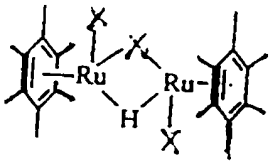

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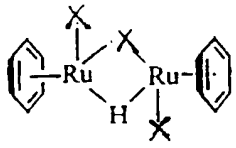

(10)

wherein X is Cl, Br or I.

4. The process for preparing a chiral ester according to any one of claim 1 to claim 3, wherein X is Cl.

5. The process for preparing a chiral ester according to claim 1, wherein said lipase is selected from the group consisting of *Pseudomonas cepacias* lipase and *Candida antarctica* component B lipase.

6. The process for preparing a chiral ester according to claim 1, wherein said acyl donor compound is aryl ester.

7. The process for preparing a chiral ester according to claim 6, wherein said aryl ester is selected from the group consisting of *p*-chlorophenyl acetate and alkenyl acetate.

8. The process for preparing a chiral ester according to claim 1, wherein said hydride donor compound is selected from the group consisting of 2,6-dimethylhepthan-4-ol, hydrogen and formic acid.

9. The process for preparing a chiral ester according to claim 1, wherein a content of said ruthenium complex is in the range of 0.1 to 5 mol%, relative to said ketone.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/01171

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07C 67/00, C12P 7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

C07C, C12P

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)

STN(REGISTRY, CAPLUS)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T, A	Novel synthetic routes to several new, differentially substituted ruthenium tris(4,4'-disubstituted-2,2-bipyridine) complexes, Dusan Hsek et al, page 308-316, American Chemical Society(2000), 39(2) see the scheme 1 and table 1	1-9
T, A	Catalytic asymmetric and chemoselective aerobic oxidation : kinetic resolution of sec-alcohols, Masutani K. et al, page 5119-5123, Tetrahedron letters (2000) 41(26) see the page 5120(reaction, scheme) and table1	1-9
T, A	synthesis of ruthenium complexes with planar-chiral cyclopentadienyl-pyridine or -phosphine bidentate ligands, Noriko Dodo et al, page 35-41, Dalton (2000) 1, Royal Society of chemistry see teh scheme 2 and 5	1-9
A	EP-A2-375417 see the whole document	1-9
P, A	EP-A1-992481 see the whole document	1-9
A	Ruthenium(2)-catalyzed asymmetric transfer hydorgenation of ketones using a formic acid-triethylamine mixture, Fujii, Akio et al, page 2521-2, American Chemical Society (1996),	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevence

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 FEBRUARY 2001 (09.02.2001)	12 FEBRUARY 2001 (12.02.2001)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR00/01171

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2-375417	1990.6.27	JP-A2-02-169555	1990.6.29
EP-A1-992481	2000.4.12	DE-A1-1998-5517	2000.4.6
		JP-A2-2000-119217	2000.4.25

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